DOCKET NO: 270280US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
MAURO NAPOLETANO, ET AL.	: EXAMINER: PESELEV, ELLI
SERIAL NO: 10/531,462	:
FILED: APRIL 15, 2005	: GROUP ART UNIT: 1623
FOR: 9A-AZALIDES WITH ANTI-INFLAMMATORY ACTIVITY	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal of the Final Rejection dated August 21, 2007 of Claims 1-15. A Notice of Appeal was filed December 21, 2007.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Zambon Group S.P.A. having an address at Via Della Chimica, 9, Vicenza 36100, Italy.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and the assignee are aware of no appeals, interferences, or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 1-15 stand rejected and are herein appealed. Claim 16 has been canceled.

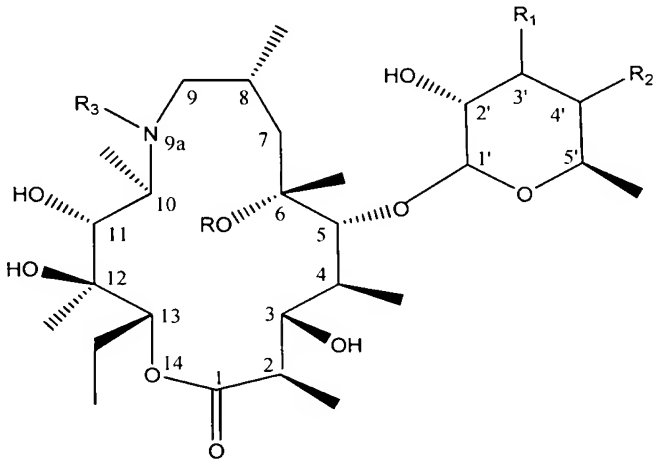
IV. STATUS OF THE AMENDMENTS

No amendment under 37 CFR 1.116 has been filed.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

A summary of the claimed subject matter, as claimed in sole independent and original Claim 1, is mapped out below, with reference to page and line numbers in the specification added in **[bold]** after each element.

The claimed subject matter is compound **[page 5, line 23]** of formula **[page 6, line 1]**



(I)

in which

R is a hydrogen atom or a methyl **[page 6, line 3]**

R_1 is a hydrogen atom, an N,N-di-(C_1-C_3)-alkylamino group, an N,N-di-(C_1-C_3)-alkylamino-N-oxide group, an N-(C_1-C_4)-acyl-N-(C_1-C_3)-alkylamino group or together with R_2 forms a bond between the carbon atoms at 3' and 4'; **[page 6, lines 4-7]**

R_2 is a hydrogen atom or together with R_1 forms a bond between the carbon atoms at 3' and 4'; **[page 6, lines 8-9]**

R_3 is a linear or branched C_1-C_5 alkyl, a benzyl optionally substituted with one or two substituents selected from nitro, hydroxy, carboxy, amino, linear or branched C_1-C_5 alkyl, C_1-C_4 alkoxy groups, C_1-C_4 alkoxycarbonyl groups, aminocarbonyl groups or cyano or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$ **[page 6, lines 10-15]**

in which

A is a hydrogen atom, a phenyl or a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur; **[page 6, lines 17-19]**

X represents O, S, SO, SO_2, NR_6 and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl, a C_1-C_3 alkoxycarbonyl group, a benzyloxycarbonyl group; **[page 6, line 20 to page 7, line 1]**

Y is a C_6H_4 group, a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur or represents O, S, SO, SO_2, NR_6 where R_6 has the meanings given above; **[page 7, lines 2-5]**

r is an integer of from 1 to 3; **[page 7, line 6]**

m is an integer of from 1 to 6; **[page 7, line 7]**

n is an integer of from 0 to 2; **[page 7, line 8]**

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form; **[page 7, lines 9-10]**

and their pharmaceutically acceptable salts; **[page 7, line 11]**

provided that when R is a hydrogen atom and R_1 is a dimethylamino group, R_3 is different from a (C_1-C_5)-alkyl group. **[page 7, lines 12-13]**

VI. GROUNDS OF REJECTION

Claims 1-15 stand rejected under 35 U.S.C. §103(a) as unpatentable over US 6,262,030 (Wu et al) in view of US 4,886,792 (Djokic et al).

VII. ARGUMENT

Claims 1-15 stand rejected under 35 U.S.C. §103(a) as unpatentable over Wu et al in view of Djokic et al. That rejection is untenable and should not be sustained.

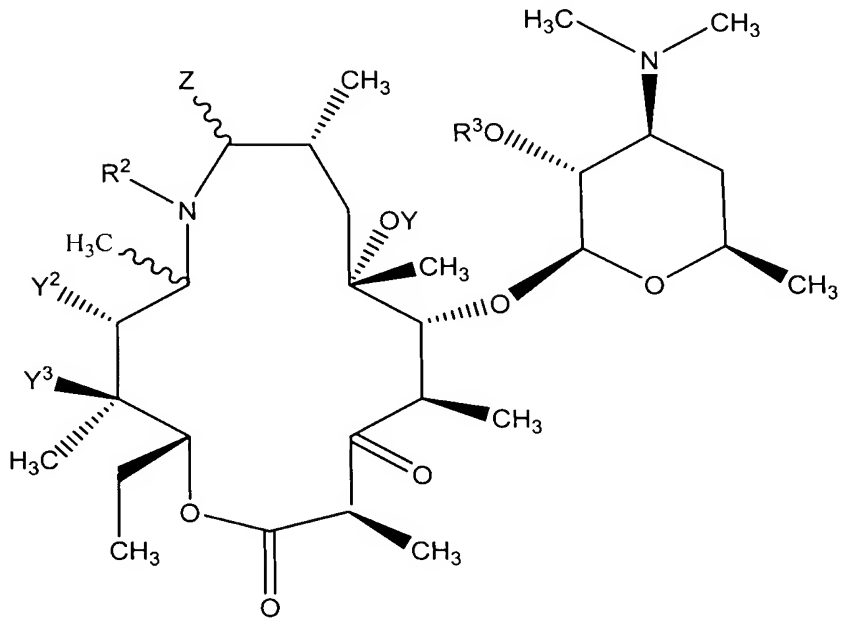
As recited in Claim 1, the embodiment of the independent claim is a 9a-azalide compound having a macrolide structure that exhibits anti-inflammatory activity while at the same time having substantially no antibiotic properties, wherein cladinose in position 3 has been removed therefrom, as described in the specification at page 5, lines 19-22.

(Applicants use the same nomenclature as Wu et al in reference to the position numbering of the macrolide nucleus.)

As described in the specification beginning at page 1, line 9, it is known that many antibiotics possess anti-inflammatory properties in addition to antibiotic properties. Azithromycin is the prototype of a class of antibiotic macrolides commonly called azilides that are widely used in the treatment of various infections, as stated. In addition, macrolides have found efficacy in pathologies in which the traditional anti-inflammatory drugs, such as corticosteriods, have proved ineffective. However, by applying the known macrolides to treat inflammation not caused by pathogenic microorganisms, the risk of rapid development of resistant strains increases. Thus, it is desirable to find new compounds with macrolide structure that exhibit anti-inflammatory activity but at the same time do not have antibiotic properties. The present invention is one such group of compounds.

Wu et al discloses various erythromycin derivatives, of various formulae, described as useful as antibacterial agents and antiprotozoa agents and for other applications, such as anti-

cancer, atherosclerosis, gastric motility reduction, etc. (column 4, lines 10-13). The Examiner relies on such derivatives having the structure of formula 5 therein (column 8):



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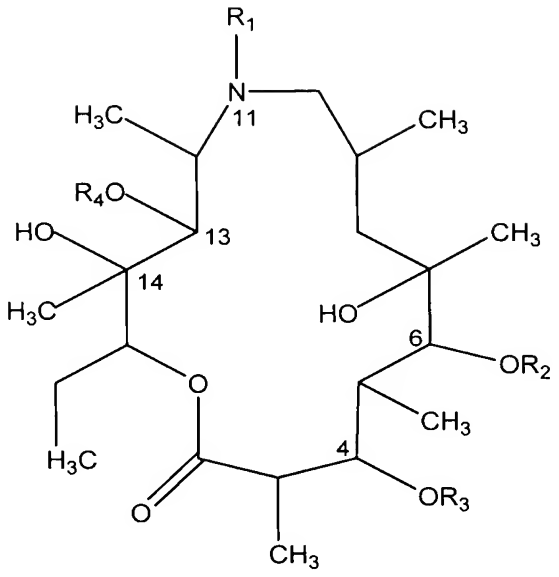
wherein, *inter alia*, there is an oxo group at the 3-position, and at the 11- position, Y^2 is defined as a C_1-C_{16} alkoxy group, -C(O)NH(C_1-C_{16}) alkyl, or -OC(O)NH(C_1-C_{16} alkyl), wherein the alkyl moieties of the Y^2 groups are optionally substituted by an R_{12} group or 1 to 3 halo groups or together Y^2 and Y^3 (at the 12-position) are taken together to form an oxazolidin-2-one ring. Thus, the compounds of the present invention differ from Wu et al at least at the 3- and 11- positions.

Djokic et al is drawn to 10-dihydro-10-deoxy-11-azaerythronolide A compounds, having anti-inflammatory activity (column 4, lines 64-67). The compounds of Djokic et al presumably have no antibiotic properties (column 1, lines 17-29). The anti-inflammatory compounds of Djokic et al have a formula (I) therein:



(I)

wherein, using the nomenclature of the present invention and of Wu et al, there may be an OH group at the 3-position (4-position using the nomenclature of Djokic et al) when R_3 is hydrogen (column 2, lines 16-18). The anti-inflammatory agent of formula (I) may be derived from a compound wherein the moiety at the 3-position is an OR'_3 group, wherein R'_3 is a cladinosyl group, and the moiety at the 5-position is an OR'_2 group, wherein R'_2 is a desosaminyl group, as shown in formula (II) therein (column 2, lines 22-41).

The Examiner finds that Wu et al's compounds are "closely analogous azithromycin antibiotics" but do not disclose antibiotics having a hydroxy group at the 3-position. The Examiner further finds that Djokic et al discloses "closely analogous antibiotics having hydroxyl group at the 3-position". The Examiner then holds that it would have been obvious to modify the compounds of Wu et al at the 3-position to have a hydroxyl group, because "such a person would have expected the resulting compounds to have antibiotic activity".

In reply, the Examiner is incorrect on many levels. As discussed above, Wu et al is directed to compounds having antibiotic activity, with no accompanying disclosure that the compounds also have anti-inflammatory activity. Djokic et al is drawn to compounds having anti-inflammatory activity but no significant, if any, antibiotic activity. Thus, there would be

absolutely no reason for one skilled in the art to consult the teachings of one reference in order to solve problems or improve the compounds of the other reference, and vice versa. Moreover, even if one skilled in the art were to combine Wu et al and Djokic et al, the result would still not be the presently-claimed invention. As discussed above, the presently-claimed compound and the compounds of formula 5 of Wu et al differ at least in the groups at both the 3-position and the 11-position.

While Wu et al may exemplify compounds having an OH group at the 11-position, as shown at columns 55-56, these are intermediate compounds and otherwise differ from the presently-claimed compounds in other ways. For example, compound 7A still has the cladinose unit at the 3-position, compounds 12A and 13A have a different substitution at the 2'-position, and compounds 14A and 15A again have a different substitution at the 11-position.

There is **no** evidence supporting the Examiner's finding that, relying on Djokic et al, that "azithromycin compound wherein only cladinose sugar is removed and which contain [sic] a hydroxy group at the 3-position was known in the art at the time the claimed invention was made."

Indeed, Djokic et al attribute the activity of their compound to the removal of both the cladinosyl and desosaminyl residue from the corresponding azithromycin derivative. Djokic et al discloses that at concentration of 10^{-5} DESAZ, i.e., the azithromycin derivative obtained from the removal of the cladinosyl residue only, shows an approximate equal activity as D-PEN at a concentration of 10^{-7} (column 5, lines 10-12). This means that DESAZ requires a concentration of two magnitude orders higher than the concentration of D-PEN to have similar activity. AZER, i.e., the azithromycin derivative obtained from the removal of both cladinosyl and desosaminyl residues, has a similar activity as D-PEN or at a concentration of 10^{-7}, a stronger one (column 5, lines 18-19). From the Diagram 3 of Djokic et al, the *in vivo*

activity of DESAZ is lower than D-PEN and DICL and far lower than the *in vivo* activity of AZER.

Accordingly, there is indication that the activity in Djokic et al is linked to the removal of both cladinosyl and desosaminyl residues. Thus, even if there had been motivation to modify the compounds of Wu et al at all in view of Djokic et al, and Applicants submit there would have been no motivation, nevertheless, the motivation would have been to also remove the desosaminyl residue at the 5-position, in view of Djokic et al and perhaps obtain compounds having improved anti-inflammatory activity.

It is clear that the Examiner has engaged in hindsight, using the present disclosure as a guide, in combining Wu et al and Djokic et al. But, as discussed above, such a combination does not result in the presently-claimed invention.

For all the above reasons, it is respectfully requested that this rejection be REVERSED.

VIII. CONCLUSION

For the above reasons, it is respectfully requested that all the rejections still pending in the Final Rejection be REVERSED.

Respectfully submitted,

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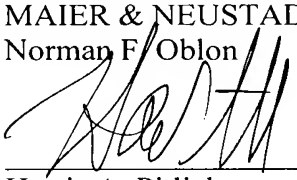
MAIER & NEUSTADT, P.C.
Norman F. Oblon



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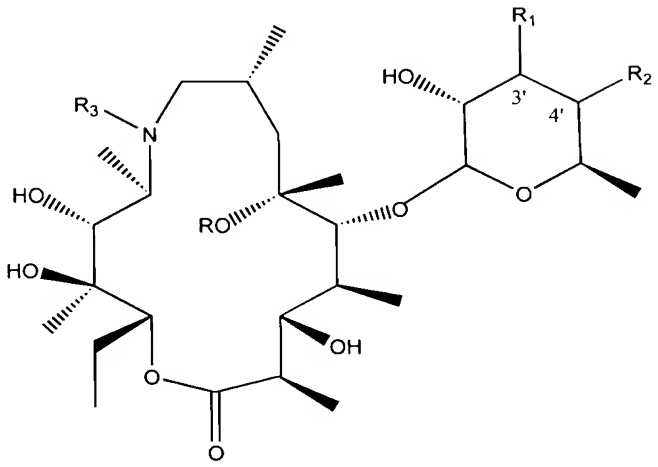
CLAIMS APPENDIX

Claim 1: A compound of formula



(I)

in which

R is a hydrogen atom or a methyl

R_1 is a hydrogen atom, an N,N-di-(C_1-C_3)-alkylamino group, an N,N-di-(C_1-C_3)-alkylamino-N-oxide group, an N-(C_1-C_4)-acyl-N-(C_1-C_3)-alkylamino group or together with R_2 forms a bond between the carbon atoms at 3' and 4';

R_2 is a hydrogen atom or together with R_1 forms a bond between the carbon atoms at 3' and 4';

R_3 is a linear or branched C_1-C_5 alkyl, a benzyl optionally substituted with one or two substituents selected from nitro, hydroxy, carboxy, amino, linear or branched C_1-C_5 alkyl, C_1-C_4 alkoxy groups, C_1-C_4 alkoxycarbonyl groups, aminocarbonyl groups or cyano or a chain of formula

$$-(CH_2)r\text{-}X\text{-}(CH_2)m\text{-}Y\text{-}(CH_2)n\text{-}A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur;

X represents O, S, SO, SO_2, NR_6 and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl, a C_1-C_3 alkoxycarbonyl group, a benzyloxycarbonyl group;

Y is a C_6H_4 group, a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur or represents O, S, SO, SO_2, NR_6 where R_6 has the meanings given above;

r is an integer of from 1 to 3;

m is an integer of from 1 to 6;

n is an integer of from 0 to 2;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form;

and their pharmaceutically acceptable salts;

provided that when R is a hydrogen atom and R_1 is a dimethylamino group, R_3 is different from a (C_1-C_5)-alkyl group.

Claim 2: A compound according to claim 1 in which R_1 is a hydrogen atom, an N-methyl-N-(C_1-C_3)-alkylamino group, an N-methyl-N-(C_1-C_3)-alkylamino-N-oxide group, an N-(C_1-C_4)-acyl-N-methylamino group or R_1 together with R_2 forms a bond between the carbon atoms at 3' and 4'.

Claim 3: A compound according to claim 2 in which R_1 is a hydrogen atom, an N,N-dimethylamino group, an N,N-dimethylamino-N-oxide group, an N-acetyl-N-methylamino group or R_1 together with R_2 forms a bond between the carbon atoms at 3' and 4'.

Claim 4: A compound according to claim 1 in which R_3 is a linear or branched (C_1-C_3) alkyl, a benzyl optionally substituted with one or two substituents selected from nitro, hydroxy, carboxy, amino, linear or branched (C_1-C_3) alkyl, C_1-C_4 alkoxy and cyano groups or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur;

X is O or NR_6 and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl;

Y, when n is 0, is a C_6H_4 group or a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur; or, when n is different from 0, it is O or NR_6 and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl;

r is an integer of from 1 to 3;

m is an integer selected from 1 and 2;

n is an integer of from 0 to 2;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form.

Claim 5: A compound according to claim 4 in which R_3 is a methyl, a benzyl or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl with five or six members selected from pyrrole, thiophene, furan, imidazole, oxazole, thiazole, pyridine, pyrimidine, triazole and thiadiazole;

X is O or NR_6 and R_6 is a hydrogen atom;

Y, when n is 0, is a C_6H_4 group or a heteroaryl with five or six members selected from pyrrole, thiophene, furan, imidazole, oxazole, thiazole, pyridine, pyrimidine, triazole and thiadiazole; or, when n is 1, it is NR_6 and R_6 is a hydrogen atom;

r is an integer of from 1 to 3;

m is an integer selected from 1 and 2;

n is an integer selected from 0 and 1;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form.

Claim 6: A compound according to claim 5 in which R_3 is a methyl, a benzyl or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl selected from thiophene, furan, imidazole, thiazole, pyridine and triazole;

X is NR_6 and R_6 is a hydrogen atom;

Y, when n is 0, is a C_6H_4 group or a heteroaryl selected from thiophene, furan, imidazole, thiazole, pyridine and triazole; or, when n is 1, it is NR_6 and R_6 is a hydrogen atom;

r is 3;

m is an integer selected from 1 and 2;

n is an integer selected from 0 and 1;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form.

Claim 7: A compound according to claim 1, in which R_1 is a hydrogen atom, an N-methyl-N-(C_1-C_3)-alkylamino group, an N-methyl-N-(C_1-C_3)-alkylamino-N-oxide group, an

N-(C_1-C_4)-acyl-N-methylamino group or R_1 together with R_2 forms a bond between the carbon atoms at 3' and 4';

at the same time R_3 is a linear or branched (C_1-C_3) alkyl, a benzyl optionally substituted with one or two substituents selected from nitro, hydroxy, carboxy, amino, linear or branched (C_1-C_3) alkyl, C_1-C_4 alkoxy and cyano groups or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur;

X is O or NR_6 and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl;

Y, when n is 0, is a C_6H_4 group or a heteroaryl with five or six members containing from one to three atoms selected from nitrogen, oxygen and sulfur; or, when n is different from 0, it is O or NR_6 and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl;

r is an integer of from 1 to 3;

m is an integer selected from 1 and 2;

n is an integer of from 0 to 2;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form.

Claim 8: A compound according to claim 7 in which R_3 is a methyl, a benzyl or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl with five or six members selected from pyrrole, thiophene, furan, imidazole, oxazole, thiazole, pyridine, pyrimidine, triazole and thiadiazole;

X is O or NR_6 and R_6 is a hydrogen atom;

Y, when n is 0, is a C_6H_4 group or a heteroaryl with five or six members selected from pyrrole, thiophene, furan, imidazole, oxazole, thiazole, pyridine, pyrimidine, triazole and thiadiazole; or, when n is 1, it is NR_6 and R_6 is a hydrogen atom;

r is an integer of from 1 to 3;

m is an integer selected from 1 and 2;

n is an integer selected from 0 and 1;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form.

Claim 9: A compound according to claim 8 in which R_3 is a methyl, a benzyl or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

in which

A is a hydrogen atom, a phenyl or a heteroaryl selected from thiophene, furan, imidazole, thiazole, pyridine and triazole;

X is NR_6 and R_6 is a hydrogen atom;

Y, when n is 0, is a C_6H_4 group or a heteroaryl selected from thiophene, furan, imidazole, thiazole, pyridine and triazole; or, when n is 1, it is NR_6 and R_6 is a hydrogen atom;

r is 3;

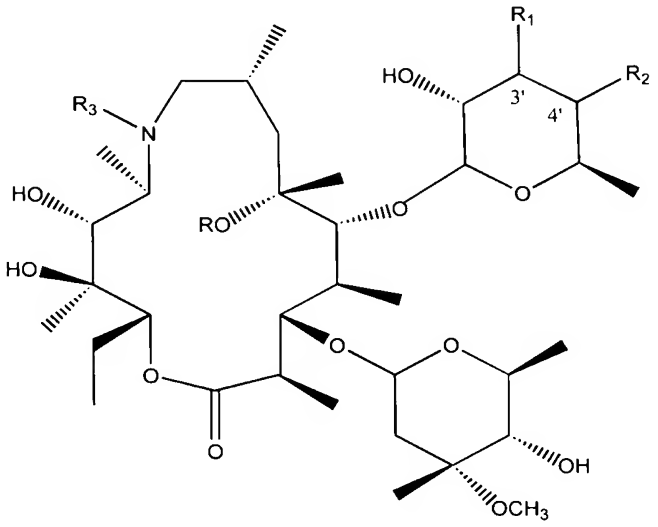
m is an integer selected from 1 and 2;

n is an integer selected from 0 and 1;

moreover the nitrogen atom to which R_3 is bound can be present in the N-oxide form.

Claim 10: A compound according to claim 9 in which R_1 is a hydrogen atom, an N,N-dimethylamino group, an N,N-dimethylamino-N-oxide group, an N-acetyl-N-methylamino group or R_1 together with R_2 forms a bond between the carbon atoms at 3' and 4'.

Claim 11: A process for preparing a compound according to claim 1 that comprises the removal of the L-cladinose at position 3, through a reaction of hydrolysis, from the azithromycin derivatives of formula



(II)

in which

R, R_1, R_2 and R_3 are defined as in claim 1.

Claim 12: A process according to claim 11 in which, in formula II, the substituent R_3 is a methyl.

Claim 13: A process according to claim 11 in which the removal of cladinose is effected through a reaction of catalyzed acid hydrolysis in the presence of an inorganic acid and a protic organic solvent.

Claim 14: A pharmaceutical composition containing a therapeutically effective quantity of a compound according to claim 1 mixed with a pharmaceutically acceptable vehicle.

Claim 15: A pharmaceutical composition according to claim 14 that can be used for treating inflammatory pathologies.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.